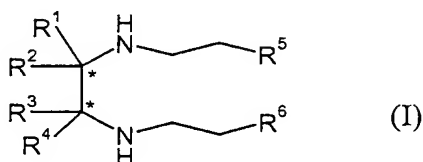


There was therefore a need to develop further catalysts and ligands which facilitate the asymmetric reduction of ketones in good yields and good optical purities.

5

SUMMARY OF THE INVENTION

In accordance with the foregoing, the present invention encompasses compounds of the formula (I)



10

where

* marks stereogenic carbon atoms which each independently have R- or S-configuration, excluding meso-compounds and

15

R^1 , R^2 , R^3 and R^4 are each independently hydrogen, C_1 - C_{12} -alkyl, C_4 - C_{24} -aryl or C_5 - C_{25} -arylalkyl, or R^1 , R^2 , R^3 and R^4 together with the ethylene bridge are 1,2-(C_5 - C_8 -cycloalkyl) and

20 R^5 and R^6 are each independently radicals which are selected from the group of $-COOR^7$, $-CONR^8R^9$, $-CN$ or $-PO(OR^{10})_2$ where R^7 , R^8 , R^9 and R^{10} are each C_1 - C_{12} -alkyl, C_4 - C_{24} -aryl or C_5 - C_{25} -arylalkyl, or NR^8R^9 as a whole is a cyclic amino radical having a total of 4 to 12 carbon atoms.

25 For the purposes of the invention, all radical definitions, parameters and illustrations hereinabove and listed hereinbelow, in general or within areas of preference, and thus also the particular areas and areas of preference, may be combined as desired.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the formula (I) have different stereoisomers. The invention encompasses both the pure stereoisomers and any desired mixtures of stereoisomers, for example racemates.

Alkyl is in each case independently a straight-chain, cyclic, branched or unbranched alkyl radical. The same applies to the nonaromatic moiety of an aryl-alkyl radical.

C₁-C₄-Alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl, C₁-C₈-alkyl is additionally, for example, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 1-ethylpropyl, cyclohexyl, cyclopentyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1-ethyl-2-methylpropyl, n-heptyl and n-octyl, and C₁-C₁₂-alkyl is further additionally, for example, adamantyl, n-nonyl, n-decyl and n-dodecyl.

Aryl is in each case independently aromatic or a heteroaromatic radical having 4 to 24 framework carbon atoms, of which no, one, two or three framework carbon atoms per cycle, but at least one framework carbon atom in the entire molecule, may be substituted by heteroatoms selected from the group of nitrogen, sulphur or oxygen, but is preferably a carbocyclic aromatic radical having 6 to 24 framework carbon atoms.

Examples of carbocyclic aromatic radicals having 6 to 24 framework carbon atoms are phenyl, naphthyl, phenanthrenyl, anthracenyl or fluorenyl, and heteroaromatic radicals having 4 to 24 framework carbon atoms, of which no, one, two

or three framework carbon atoms per cycle, but at least one framework carbon atom in the entire molecule, may be substituted by heteroatoms selected from the group of nitrogen, sulphur or oxygen, are, for example, pyridinyl, benzofuranyl, dibenzofuranyl or quinolinyl.

5

The carbocyclic aromatic radical or heteroaromatic radical may also be substituted by up to five identical or different substituents per cycle which are selected from the group of chlorine, fluorine, C₁-C₁₂-alkyl, C₁-C₁₂-alkoxy, di(C₁-C₈-alkyl)amino, COO(C₁-C₈-alkyl), CON(C₁-C₈-alkyl)₂, COO(C₁-C₈-alkyl),
 10 COO(C₄-C₁₄-aryl), CO(C₁-C₈-alkyl), C₅-C₁₅-arylalkyl or tri(C₁-C₆-alkyl)siloxyl.

C₄-C₂₄-Aryl is, for example and with preference, phenyl, o-, p-, m-tolyl, o-, p-, m-anisyl, o-, p-, m-fluorophenyl, o-, p-, m-chlorophenyl, o-, p-, m-trifluoromethylphenyl, o-, p-, m-nitrophenyl and 2-, 3- and 4-pyridyl.

15

Arylalkyl is in each case independently a straight-chain, cyclic, branched or unbranched alkyl radical as defined above which may be singly, multiply or fully substituted by aryl radicals as defined above.

20 C₅-C₁₅-Arylalkyl is, for example and with preference, benzyl or (R)- or (S)-1-phenylethyl.

The preferred substitution patterns for compounds of the formula (I) are defined hereinbelow:

25

R¹, R², R³ and R⁴ are preferably each independently hydrogen, C₁-C₈-alkyl or C₄-C₂₄-aryl, or R¹, R², R³ and R⁴ together with the ethylene bridge are each 1,2-cyclohexylene.

30 R¹, R², R³ and R⁴ together with the ethylene bridge are particularly preferably 1,2-dimethyl-1,2-ethylene, 1,2-diphenyl-1,2-ethylene or 1,2-cyclohexylene, very

particularly preferably (R,R)- and (S,S)-1,2-diphenyl-1,2-ethylene or (R,R)- and (S,S)-1,2-cyclohexylene.

5 R^5 and R^6 are preferably each independently, but more preferably identically, radicals selected from the group of $-\text{COOR}^7$, $-\text{CONR}^8\text{R}^9$, $-\text{CN}$ or $-\text{PO}(\text{OR}^{10})_2$, where R^7 , R^8 , R^9 and R^{10} are each C_1 - C_4 -alkyl or C_4 - C_{24} -aryl.

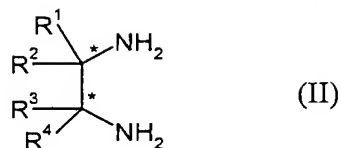
R^5 and R^6 are each very particularly preferably $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$, $-\text{CN}$, $-\text{CON}(\text{CH}_3)_2$, $-\text{CON}(\text{C}_2\text{H}_5)_2$, $-\text{PO}(\text{OCH}_3)_2$, $-\text{PO}(\text{OC}_2\text{H}_5)_2$ and $-\text{PO}(\text{Ophenyl})_2$.

10

Particularly preferred compounds of the formula (I) are as follows:

(1S,2S)- and (1R,2R)-bis-[N-(2-dimethylphosphonatoethyl)amino]cyclohexane,
 (1S,2S)- and (1R,2R)-bis-[N-(2-diethylphosphonatoethyl)amino]cyclohexane,
 15 (1S,2S)- and (1R,2R)-bis-[N-(2-diphenylphosphonatoethyl)amino]cyclohexane,
 (1S,2S)- and (1R,2R)-bis-[N-(2-cyanoethyl)amino]cyclohexane, (1S,2S)- and
 (1R,2R)-bis-[N-(2-carboxylethylethyl)amino]cyclohexane and (1S,2S)- and
 (1R,2R)-bis-[N-(2-carboxylmethylethyl)amino]cyclohexane, (1S,2S)- and
 (1R,2R)-bis-[N-(2-dimethylphosphonatoethyl)amino]-1,2-diphenylethane,
 20 (1S,2S)- and (1R,2R)-bis-[N-(2-diethylphosphonatoethyl)amino]-1,2-
 diphenylethane, (1S,2S)- and (1R,2R)-bis-[N-(2-
 diphenylphosphonatoethyl)amino]-1,2-diphenylethane, (1S,2S)- and (1R,2R)-bis-
 [N-(2-cyanoethyl)amino]-1,2-diphenylethane, (1S,2S)- and (1R,2R)-bis-[N-
 (2-carboxyethylethyl)amino]-1,2-diphenylethane, (1S,2S)- and (1R,2R)-bis-[N-
 25 (2-carboxymethylethyl)amino]-1,2-diphenylethane.

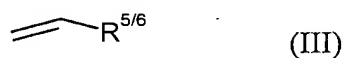
The compounds of the formula (I) according to the invention can be prepared in a manner known per se (see WO-A 00/24751), for example, by reacting amines of the formula (II)



where

*, R¹, R², R³ and R⁴ are each as defined under formula (I), including their areas of
5 preference,

with compounds of the formula (III)



10

where

R⁵ and R⁶ are each as defined under formula (I), including their areas of
preference.

15

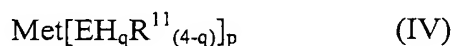
The invention also encompasses catalysts which comprise transition metal
complexes of compounds of the formula (I).

The ratio of transition metal to compound of the formula (I) is preferably 0.05 to
20 2.0, particularly preferably 0.1 to 1.5 and very particularly 0.9 to 1.1.

Transition metal complexes of compounds of the formula (I) are preferably zinc
and cobalt complexes of compounds of the formula (I).

25 Particularly preferred transition metal complexes of compounds of the formula (I)
are those which are obtainable by reacting halides, carbonates, cyanurates,
isocyanates, sulphates, phosphates, nitrates, carboxylates or alkoxides of zinc or
cobalt with compounds of the formula (I).

Such transition metal complexes are preferably reacted with reducing agents before they are used as a catalyst. Examples of suitable reducing agents include hydrides of alkali metals and alkaline earth metals or aluminium-hydrogen or boron-hydrogen compounds, in particular those of the formula (IV)



where

10

Met is a mono- or bivalent metal, preferably zinc, lithium, sodium or potassium and

E is aluminium or boron and

15

R¹¹ is C₁-C₈-alkyl and

q is 1, 2, 3 or 4, preferably 4 or 1, and

20

p is the valency of Met.

Very particularly preferred reducing agents are LiBH₄, NaBH₄, Zn(BH₄)₂, LiAlH₄, Li[BHethyl₃] and Li[AlH(sec-butyl)₃], Na[AlH₂(2-methoxyethoxy)₂], sodium hydride and lithium hydride.

25

The amount of the reducing agent is preferably selected in such a way that the molar ratio of hydridic hydrogen in the reducing agents to the transition metal complex is 0.5 to 5. Larger ratios are possible but uneconomic.

30

Further particularly preferred transition metal complexes are those which are obtained by reacting compounds of the formula (I) with zinc compounds ZnY₂ or

ZnYHal where Y is in each case independently hydrogen, BH₄ or an organic radical, for example and with preference, C₁-C₈-alkyl phenyl, and Hal is bromine, chlorine or iodine.

- 5 Preferred zinc compounds ZnY₂ are dimethylzinc, diethylzinc, dibutylzinc, diphenylzinc and zinc hydride. Examples of preferred zinc compounds ZnYHal are phenylzinc chloride, methylzinc chloride and ethylzinc chloride.

10 These further preferred transition metal complexes can be used directly as catalysts.

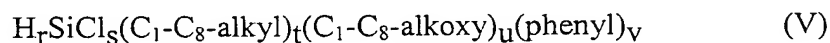
The invention also encompasses a process for asymmetrically reducing ketones with silanes in the presence of catalysts, which is characterized in that the catalysts used are those which comprise transition metal complexes of compounds of the
15 formula (I).

The definitions, including their areas of preference, specified for the transition metal complexes and for the compounds of the formula (I) apply correspondingly.

- 20 Transition metal complexes of compounds of the formula (I) can either be used as isolated complexes or, in a preferred procedure, prepared directly in the reaction mixture.

Preferred silanes are those of the formula (V)

25



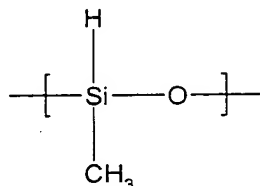
where

- 30 r is one, two or three

and

$$(s + t + u + v) = (4 - r)$$

- 5 or polymethylhydrosiloxane (PMHS) having the repeating structural unit



- Particular preference is given to $\text{H}_2\text{Si}(\text{C}_1\text{-C}_8\text{-alkyl})_2$, $\text{HSi}(\text{C}_1\text{-C}_8\text{-alkoxy})_3$,
 10 $\text{H}_7\text{SiCl}_5(\text{C}_1\text{-C}_8\text{-alkyl})_t$, HSiphenyl_3 , $\text{H}_2\text{Siphenyl}_2$, $\text{H}_3\text{Siphenyl}$ and PMHS, and
 even greater preference is given to PMHS.

- The amount of catalyst is advantageously selected in such a way that the molar
 ratio of transition metal, preferably zinc, to ketone used is 0.001 to 0.20,
 15 preferably 0.01 to 0.1 and particularly preferably 0.01 to 0.05.
 The reaction temperature is, for example, -20°C to 120°C , preferably 0°C to 60°C .

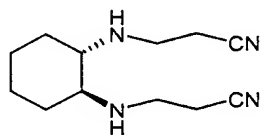
- The reaction can be carried out with or without, preferably with, solvent.
 Examples of useful solvents include ethers such as methyl tert-butyl ether,
 20 dioxane, tetrahydrofuran, ethylene glycol dimethyl ether or diisopropyl ether and
 also aliphatic or aromatic hydrocarbons, for example cyclohexane, toluene, n-
 hexane, n-heptane, petroleum ether, xylene or mesitylene.

- Preferred ketones are aryl ketones, in particular optionally substituted
 25 acetophenones, propiophenones or butyrophenones.

In the manner according to the invention, stereoisomerically enriched alcohols are obtained.

5 The stereoisomerically enriched alcohols which can be obtained according to the invention are suitable in particular in a process for preparing pharmaceuticals and agrochemicals.

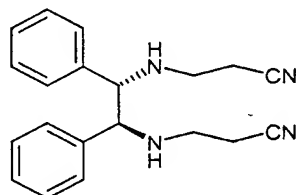
10 The advantage of the invention is that ligands and their transition metal complexes are provided which can be prepared in a simple manner and allow high yields and stereoselectivities in the asymmetric reduction of ketones.

EXAMPLES**Example 1****Preparation of (1S,2S)-bis-[N-(2-cyanoethyl)amino]cyclohexane**

5

1.0 g of (1S,2S)-(+)-diaminocyclohexane (8.8 mmol) is dissolved at room temperature in 10 ml of ethanol. 1.24 ml of acrylonitrile (1.0 g, 18.8 mmol) are added and the mixture is stirred at room temperature for 72 h. According to gas chromatography analysis, the diaminocyclohexane has been completely converted. After distillation of the alcohol, a colorless oil (1.8 g) remains which, according to gas chromatography analysis, is a homogeneous product (purity > 98%).

10

Example 2**15 Preparation of (1S,2S)-bis-[N-(2-cyanoethyl)amino]-1,2-diphenylethane**

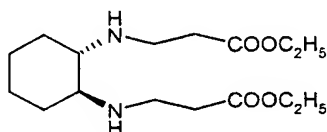
20

0.5 g of (1S,2S)-(-)-diphenylethylenediamine (2.4 mmol) is dissolved in 10 ml of ethanol. After the addition of 0.32 ml of acrylonitrile (4.9 mmol), the mixture is stirred at room temperature for 20 h. After this time, another 0.1 ml of acrylonitrile (0.08 g, 1.5 mmol) is added and the mixture is stirred at room temperature for a further 72 h. The solvent is distilled off and the remaining oil is admixed with 5 ml of ether. The precipitated solid (0.46 g) is filtered off with

suction and dried under high vacuum. According to gas chromatography analysis, the product has a purity of 99%.

Example 3

5 Preparation of (1S,2S)-bis-[N-(2-carboxylethylethyl)amino]cyclohexane

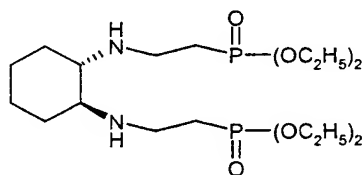


1.0 g of (1S,2S)-(-)-diaminocyclohexane (8.8 mmol) is dissolved in 50 ml of
10 ethanol, then 2.0 ml of ethyl acrylate (1.84 g, 18.4 mmol) are added. The mixture
is stirred at room temperature for 24 h. According to gas chromatography analysis,
the reactant has been completely converted. After distilling off the solvent, 2.8 g
of a colourless oil are obtained which, according to gas chromatography analysis,
has a purity of 96%.

15

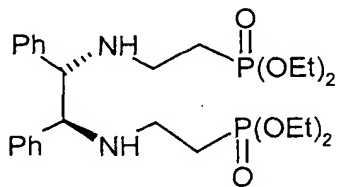
Example 4

Preparation of (1S,2S)-bis-[N-(2-diethylphosphonatoethyl)amino]cyclohexane



20

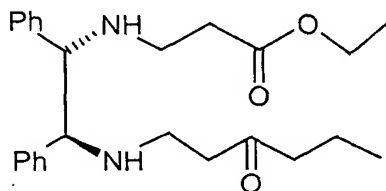
1.0 g of (1S,2S)-(-)-diaminocyclohexane (8.8 mmol) is dissolved in 10 ml of
ethanol, then 2.7 ml of diethyl vinylphosphonate (2.9 g, 17.5 mmol) are added.
The mixture is stirred at room temperature for 27 h. According to gas
chromatography analysis, the reactant has been completely converted. After
25 distilling off the solvent, 3.9 g of a colourless oil are obtained which, according to
gas chromatography analysis, has a purity of 90%.

Example 5**Preparation of (1S,2S)-bis-[N-(2-diethylphosphonatoethyl)amino]-1,2-diphenylethane**

5

2.0 g of (1S,2S)-diphenylethylenediamine (9.4 mmol) are initially charged in 50 ml of ethanol, then 3.2 ml of diethyl vinylphosphonate (20.7 mmol) are added and the mixture is heated to reflux temperature for 72 h. The ethanol is distilled off and the residue chromatographed on silica gel. Elution with ethyl acetate/methanol (5:2) provides 2.5 g of crude product which still contains vinylphosphonic ester. This material is distilled off in a Kugelrohr at 60 to 90°C and 0.1 mbar. The residue contains clean ligand (¹H NMR).

10

Example 6**15 Preparation of (1S,2S)-bis-[N-(2-carboxyethylethyl)amino]-1,2-diphenylethane**

20

2.0 g of (1S,2S)-diphenylethylenediamine (9.4 mmol) are dissolved in 50 ml of ethanol. After adding 2.2 ml of ethyl acrylate (20.7 mmol), the mixture is stirred at room temperature for 48 h. Ethanol and excess acrylic ester are distilled off under reduced pressure. The residue remaining is the desired ligand as a homogeneous compound.

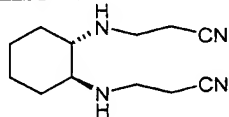
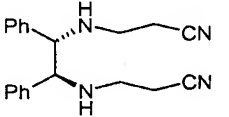
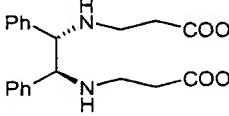
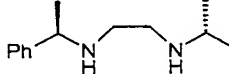
Examples 7 to 10**Asymmetric reduction of propiophenone**

A rolled flange vessel with a septum seal is evacuated and filled with argon.

- 5 0.23 mmol of a chiral ligand of Examples 1 to 6 is then weighed in and dissolved in 0.7 ml of toluene, and 0.21 ml of a 1.1M solution of diethylzinc in toluene (0.23 mmol) is added. The mixture is stirred at room temperature for 10 min, in order to form the complex from the zinc compound and the ligand. Afterwards, 1.5 ml of propiophenone (1.51 g, 11.3 mmol) and 0.90 g of
- 10 polymethylhydrosiloxane (PMHS, 13.2 mmol) are added to the reaction mixture and it is stirred at 30°C for 23 h.

- For the analysis, 0.05 ml of the reaction mixture is cautiously added dropwise to 1.5 ml of 45% aqueous KOH. 4 ml of toluene are added and the reaction product
- 15 is extracted into the organic phase. After removing the organic phase and drying over MgSO₄, gas chromatography analysis is carried out on a Chirasil® chiral column.

The results are reported in Table 1.

Example	Ligand	Yield (%)	% ee
7		68	82
8		58	82
9		78	83
10 (noninventive)		63	80

Examples 11 to 14**Asymmetric reduction of isobutyrophenone**

A rolled flange vessel with a septum seal is evacuated and filled with argon.

- 5 0.20 mmol of a chiral ligand of Examples 1 to 6 is then weighed in and dissolved in 0.62 ml of toluene, and 0.185 ml of a 1.1M solution of diethylzinc in toluene (0.20 mmol) is added. The mixture is stirred at room temperature for 10 min, in order to form the complex from the zinc compound and the ligand. Afterwards, 1.5 ml of isobutyrophenone (1.48 g, 10.0 mmol) and 0.80 g of
- 10 polymethylhydrosiloxane (PMHS, 12.3 mmol) are added to the reaction mixture and it is stirred at 30°C for 23.5 h.

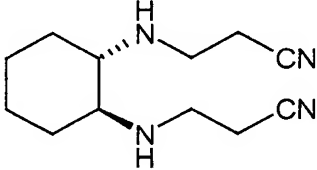
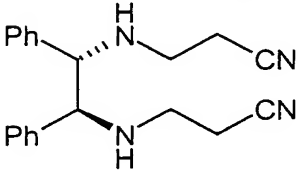
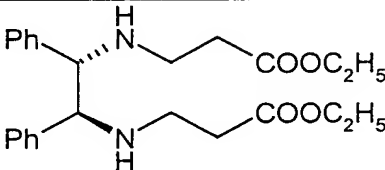
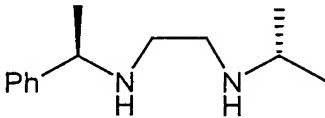
- For the analysis, 0.05 ml of the reaction mixture is cautiously added dropwise to 1.5 ml of 45% aqueous KOH. 4 ml of toluene are added and the reaction product
- 15 is extracted into the organic phase. After removing the organic phase and drying over MgSO₄, gas chromatography analysis is carried out on a Chirasil® chiral column.

20

25

30

The results are reported in Table 2.

Example	Ligand	Yield (%)	% ee
11		64	83
12		50	86
13		63	89
14 (noninventive)		61	81

Examples 15 to 17**5 Asymmetric reduction of 2-bromoacetophenone**

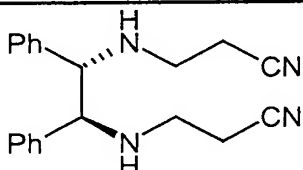
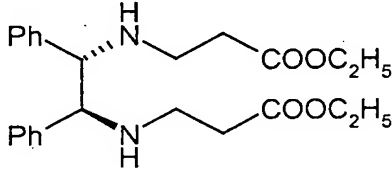
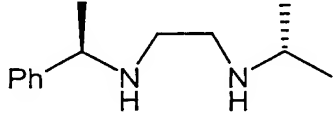
A rolled flange vessel with a septum seal is evacuated and filled with argon.

0.20 mmol of a chiral ligand of Examples 1 to 6 is then weighed in and dissolved in 0.7 ml of toluene, and 0.21 ml of a 1.1M solution of diethylzinc in toluene

10 (0.20 mmol) is added. The mixture is stirred at room temperature for 10 min, in order to form the complex from the zinc compound and the ligand. Afterwards, 1.52 ml of 2-bromoacetophenone (2.2 g, 11.3 mmol) and 0.90 g of polymethylhydrosiloxane (PMHS, 13.2 mmol) are added to the reaction mixture and it is stirred at 30°C for 23 h.

For the analysis, 0.05 ml of the reaction mixture is cautiously added dropwise to 1.5 ml of 45% aqueous KOH. 4 ml of toluene are added and the reaction product is extracted into the organic phase. After removing the organic phase and drying over MgSO₄, gas chromatography analysis is carried out on a Chirasil® chiral column.

The results are reported in Table 3.

Example	Ligand	Yield (%)	% ee
15		65	76
16		76	75
17 (noninventive)		73	71

Examples 18 to 22

Asymmetric reduction of 2-methylacetophenone

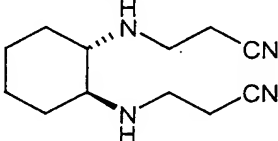
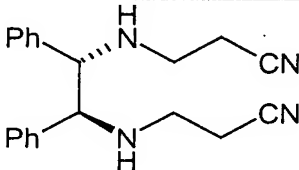
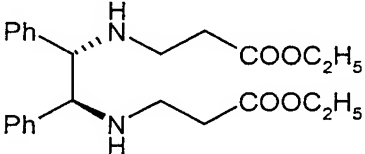
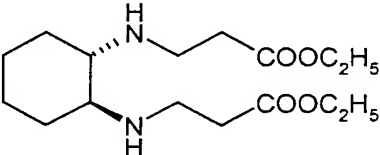
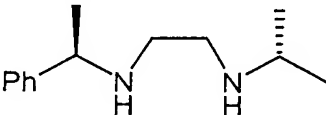
A rolled flange vessel with a septum seal is evacuated and filled with argon.

0.20 mmol of a chiral ligand of Examples 1 to 6 is then weighed in and dissolved in 0.62 ml of toluene, and 0.185 ml of a 1.1M solution of diethylzinc in toluene (0.20 mmol) is added. The mixture is stirred at room temperature for 10 min, in order to form the complex from the zinc compound and the ligand. Afterwards, 1.31 ml of 2-methylacetophenone (1.34 g, 10.0 mmol) and 0.80 g of

polymethylhydrosiloxane (PMHS, 11.8 mmol) are added to the reaction mixture and it is stirred at 30°C for 22 h.

For the analysis, 0.05 ml of the reaction mixture is cautiously added dropwise to 1.5 ml of 45% aqueous KOH. 4 ml of toluene are added and the reaction product is extracted into the organic phase. After removing the organic phase and drying over MgSO₄, gas chromatography analysis is carried out on a Chirasil® chiral column.

The results are reported in Table 4.

Example	Ligand	Yield (%)	% ee
18		85	57
19		72	60
20		72	72
21		82	61
22 (noninventive)		83	28

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may be limited by the claims.